REMARKS

Upon entry of the above amendment, claims 1-7, 10-18 and 23 will be pending in this application. Applicants respectfully submit that the amendment does not introduce new matter within the meaning of 35 U.S.C. §132. Accordingly, entry of the amendment is respectfully requested.

1. Rejection of claims 1-7, 10-18 and 23 under 35 USC 112, 1st paragraph

The Official Action states that claims 1-7, 10-18 and 23 are rejected under 35 USC 112, 1st paragraph as failing to comply with the written description requirement.

In particular, the Official Action states that "there is no proof that the applicant was in possession of all the derivatives of BH4, except for those contained within the [specification]." Further, the Official Action states that there is not sufficient written description for the phrase "arginine or a derivative thereof".

Applicants respectfully traverse this rejection. However, solely to remove the basis for the rejection of these claims, applicants have amended the claims to recite BH4 and specific derivatives thereof that have clear written description in the specification at pages 3-5. Likewise, applicants have amended the claims to recite arginine and specific derivatives thereof that have clear written description in the specification at page 10. As such, all pending claims have clear written description in the instant specification.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

2. Rejection of claims 1-7 and 11-15 under 35 USC 112, 1st paragraph

The Official Action states that claims 1-7 and 11-15 are rejected under 35 USC 112, 1st paragraph as being non-enabled. In particular, the Examiner alleges that, while the specification is enabling for claims directed to treating a respiratory disease, it is not enabling for claims directed to preventing a respiratory disease.

Applicants respectfully traverse this rejection. However, solely to remove the basis for this rejection, applicants have deleted the rejected language from the claims without prejudice. In particular, all references to "preventing" a disease have been removed from the claims.

Accordingly, the basis of this rejection has been rendered moot and applicants respectfully request that the Examiner reconsider and withdraw this rejection.

3. Rejection of Claims 1-2 and 10 under 35 U.S.C. § 102(b)

The Official Action states that claims 1-2 and 10 stand rejected under 35 U.S.C. §102(b) as being anticipated by Schmid et al. (WO 01/56551). In particular, the Official Action states that:

> For instant claims 1-2, Schmid, et al. teach a method useful for preventing or reversing acute pulmonary vasoconstriction, such as may result from pneumonia, inflammation of the lung, as well as those cases of chronic pulmonary vasoconstriction which have a reversible component, comprising the use of BH4.
>
> Instant claim 10 recites a commercial product comprising a pharmaceutical preparation of BH4 or a derivative thereof. For instant claim 10, Schmid et al. teach: a pharmaceutical composition comprising BH4.

Applicants respectfully traverse this rejection. The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP § 2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

Applicants respectfully direct the Examiner's attention to the full scope of claims 1-2 and 10. Of particular relevance to the instant rejection is the claim limitation "...a therapeutically effective amount of [BH4]...". It is clear from the Schmid et al. reference that a synergistic combination of BH4 or a precursor thereof and membrane-permeable analogues of cGMP is required to achieve the desired effect. Particularly noteworthy is the teaching by Schmid et al. on page 8, last paragraph that

> "Because of the synergistic therapeutic effects achieved by administration of BH4 and/or a cGMP analogue, this invention provides particularly advantageous methods of achieving a therapeutic relief of vasoconstriction or improvement in the preservation and survival of transplanted organs with less than therapeutic levels of BH4 or precursor and/or cGMP membrane permeable analogues." (emphasis added)

Accordingly, it is absolutely clear that the Schmid et al. reference fails to teach each and every element of the presently claimed invention. Namely, Schmid et al. fail to teach the administration of a therapeutically effective amount of BH4 (as claimed in claims 1-2). Similarly, Schmid et al. also fail to teach a pharmaceutical composition which is "suitable

for treatment of COPD" (as claimed in claim 10) because a less than therapeutically effective amount of BH4 would not satisfy this limitation.

As such, the Schmid et al. reference fails to establish a *prima facie* case of anticipation of claims 1-2 and 10 and withdrawal of this rejection is respectfully requested.

4. Rejection of Claim 10 under 35 U.S.C. § 102(b)

The Official Action states that claim 10 stands rejected under 35 U.S.C. §102(b) as being anticipated by Takafumi et al. (EP0908182). In particular, the Official Action states that:

> Instant claim 10 recites a commercial product comprising a pharmaceutical preparation of BH4 or a derivative thereof. For instant claim 10, Takafumi et al. teach: a pharmaceutical composition comprising BH4 or a derivative thereof.

Applicants respectfully traverse this rejection. The requirements for establishing a *prima facie* case of anticipation are outlined above in section 3. The cited Takafumi et al. reference fails to meet these requirements and, thus, fails to establish a *prima facie* case of anticipation.

In particular, applicants respectfully note that the Takafumi et al. reference fails to teach that the pharmaceutical preparation is suitable for treating COPD. In fact, the Takafumi et al. reference fails to even disclose this particular disorder. As such, it cannot possibly "teach each and every element" of the presently claimed invention as required by *Verdegaal Bros. v. Union Oil Co. of California*, Id.

As such, the Takafumi et al. reference fails to establish a *prima facie* case of

anticipation of claim 10 and withdrawal of this rejection is respectfully requested.

5. Rejection of Claim 23 under 35 U.S.C. § 102(b)

The Official Action states that claim 23 stands rejected under 35 U.S.C. §102(b) as being anticipated by Schmid et al., or Takafumi et al., or Zimmerman et al. In particular, the Official Action states, in relevant part, that:

> Instant claim 23 recites a trade package comprising as pharmaceutical agent BH4 or a derivative thereof and/or arginine or a derivative thereof. For instant claim 23, Schmid et al. teach a pharmaceutical composition comprising BH4. For instant claim 23, Takafumi et al. teach a pharmaceutical composition comprising BH4 or a derivative thereof. For instant claim 23, Zimmerman et al. teaches a medicament comprising L-NMMA.

Applicants respectfully traverse this rejection. The requirements for establishing a *prima facie* case of anticipation are outlined above in section 3. It is unclear whether the Examiner is combining the teachings of three separate references in his rejection. If he is, applicants respectfully remind the Examiner that, to establish a *prima facie* case of anticipation, all of the elements of a claimed invention must be taught in a single prior art reference.

If the Examiner is alleging that claim 23 is anticipated by each of the three cited references separately, applicants respectfully note that claim 23 is not anticipated by any of these references, either separately or in combination.

The cited Schmid et al. reference fails to teach the claim limitations and, thus, fails to establish a *prima facie* case of anticipation. Applicants respectfully note that the cited

Schmid et al. reference does not contain any teaching regarding the combination of BH4 or its derivatives with arginine or its derivatives. Further, Schmid et al. fail to teach a trade package that contains instructions that BH4 and arginine could be used in combination simultaneously, separately or sequentially in the treatment of respiratory diseases.

The cited Takafumi et al. reference also fails to teach the claim limitations and, thus, fails to establish a *prima facie* case of anticipation. Applicants respectfully note that the cited Takafumi et al. reference fails to teach a trade package that contains instructions that BH4 and arginine could be used in combination simultaneously, separately or sequentially in the treatment of respiratory diseases.

Further, the cited Zimmerman et al. reference also fails to teach the claim limitations and, thus, fails to establish a *prima facie* case of anticipation. Applicants respectfully note that the cited Zimmerman et al. reference does not contain any teaching regarding the combination of BH4 or its derivatives with arginine or its derivatives. Further, Zimmerman et al. fail to teach a trade package that contains instructions that BH4 and arginine could be used in combination simultaneously, separately or sequentially in the treatment of respiratory diseases.

As such, none of the cited references, alone or in combination can possibly "teach each and every element" of the presently claimed invention as required by *Verdegaal Bros. v. Union Oil Co. of California*, Id. Therefore, the Schmid et al., Takafumi et al. and Zimmerman et al. references fail to establish a *prima facie* case of anticipation of claim 23 and withdrawal of this rejection is respectfully requested.

6. Rejection of Claims 10, 16-18 and 23 under 35 U.S.C. § 102(a)

The Official Action states that claims 10, 16-18 and 23 stand rejected under 35 U.S.C. §102(a) as being anticipated by Rabelnik et al. (US 6544994). In particular, the Official Action states that:

> Instant claims 10, 16-18 and 23 recite a commercial product or a preparation or a pharmaceutical composition or a trade package comprising BH4 or a derivative thereof, or BH4 or a derivative thereof and arginine or a derivative thereof or BH4 or a derivative thereof and/or arginine or a derivative thereof. For instant claims 10, 16-18 and 23, Rabelnik et al. teach: a pharmaceutical composition comprising at least BH4 and arginine.

Applicants respectfully traverse this rejection. The requirements for establishing a *prima facie* case of anticipation are outlined above in section 3. The cited Rabelnik et al. reference fails to meet these requirements and, thus, fails to establish a *prima facie* case of anticipation.

In particular, applicants respectfully note that the Rabelnik et al. reference fails to teach a pharmaceutical preparation which is suitable for treating respiratory diseases, much less the specific disease COPD. Instead, Rabelnik et al. focus on treatment of cardiovascular and neurological disorders. Further, Rabelnik et al. do not teach a trade package that contains instructions that BH4 and arginine could be used in combination simultaneously, separately or sequentially in the treatment of respiratory diseases. As such, it cannot possibly "teach each and every element" of the presently claimed invention as required by *Verdegaal Bros. v. Union Oil Co. of California*, Id.

As such, the Rabelnik et al. reference fails to establish a *prima facie* case of anticipation of claims 10, 16-18 and 23 and withdrawal of this rejection is respectfully

requested.

7. Rejection of claims 1-7 and 11-15 under 35 U.S.C. §103(a)

The Official Action states that claims 1-7 and 11-15 are rejected under 35 U.S.C. §103(a) over Rabelnik et al. In particular, the Official Action states that "it would have been *prima facie* obvious for a person of ordinary skill in the art to treat any respiratory disease (including COPD) using a combination of BH4 and arginine..."

Applicants respectfully traverse this rejection. To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court recently held in *KSR International Co. v. Teleflex Inc. et al.*, 127 S. Ct. 1727, 167 L.Ed. 705 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-

15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

As outlined above in section 6, applicants respectfully note that the Rabelnik et al. reference fails to teach a method for treating respiratory diseases, much less the specific disease COPD by using a combination of BH4 and arginine or their respective derivatives. Instead, Rabelnik et al. focus on treatment of cardiovascular and neurological disorders. Treatment of respiratory diseases such as COPD is completely different than those diseases taught by Rabelnik et al. For the Examiner to conclude that, based on the limited disclosure of the Rabelnik et al. reference, treatment of respiratory diseases by co-administration of BH4 and / or arginine and their respective derivatives, is impermissible hindsight reconstruction. This is a clear case of the cited reference failing to meet all of the claim limitations. Accordingly, the cited Rabelnik, et al. reference fails to teach all of the limitations of the presently pending claims, as required by *In re Wilson*.

As such, the Examiner has failed to demonstrate a *prima facie* case of obviousness against the presently pending claims. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

8. Rejection of claims 3-4 and 6 under 35 U.S.C. §103(a)

The Official Action states that claims 3-4 and 6 are rejected under 35 U.S.C. §103(a) over Schmid et al. In particular, the Official Action states that "it would have been prima facie obvious for a person of ordinary skill in the art to treat COPD using BH4 ..."

Applicants respectfully traverse this rejection. The requirements for establishing a *prima facie* case of obviousness are outlined above in section 7.

Applicants respectfully direct the Examiner's attention to the full scope of claims 3-4 and 6. Of particular relevance to the instant rejection is the claim limitation "...a therapeutically effective amount of [BH4]...". It is clear from the Schmid et al. reference that a synergistic combination of BH4 or a precursor thereof and membrane-permeable analogues of cGMP is required to achieve the desired effect. Particularly noteworthy is the teaching by Schmid et al. on page 8, last paragraph that

> "Because of the synergistic therapeutic effects achieved by administration of BH4 and/or a cGMP analogue, this invention provides particularly advantageous methods of achieving a therapeutic relief of vasoconstriction or improvement in the preservation and survival of transplanted organs with less than therapeutic levels of BH4 or precursor and/or cGMP membrane permeable analogues." (emphasis added)

Accordingly, it is absolutely clear that the Schmid et al. reference fails to teach each and every element of the presently claimed invention. Namely, Schmid et al. fail to teach the administration of a therapeutically effective amount of BH4 as claimed in claims 3-4 and 6. As such, the Schmid et al. reference fails to establish a *prima facie* case of obviousness of claims 3-4 and 6 and withdrawal of this rejection is respectfully requested.

CONCLUSION

Based upon the above amendment and remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the pending rejections and allow all pending claims of this application. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,
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Date: April 11, 2008

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